REMARKS/ARGUMENTS

I. The Amendment

Claim 1 is amended to include growth hormone releasing factor (GRF) or IL-2 in the VIP family of peptides, which includes secretin and glucagon. Support for this amendment is found in the specification at page 10, lines 10 through 19. Claim 1 is also amended to clarify that the VIP/GRF or IL-2 family of peptides may be active agents, effective in the treatment of numerous disease states recited therein. Claim 1 is also amended to remove a typographical error in the advertent omission of a comma.

Claims 15, 16, 19, 20, and 26 are amended to remove the word "products" from the phrase "multilamellar liposome products."

Claim 25 is amended because it was in improper form. Claim 25 is now a proper multiple dependent claim.

New claim 31 is supported by original claim 25.

This amendment is made solely to place the application in order for allowance and does not include new matter. The Applicants respectfully request entry of the amendment. The Applicants do not intend by this or any amendment to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

This amendment and response is timely filed along with a petition for an extension of time and the appropriate fee. Should any additional fee be deemed necessary in connection with the filing of this amendment, the Commissioner is hereby authorized to deduct any such fee from Marshall, Gerstein & Borun deposit account number 13-2855.

II. The Outstanding Rejections

The Examiner rejected claims 1-24 and 26-30 under 35 U.S.C. §112, second paragraph, for assertedly failing to particularly point out and distinctly claim the subject matter.

Claims 1-3 and 5-24 were rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure of U.S. Patent No. 5,770,570 to Paul *et al.* [hereinafter "Paul"] in view of the disclosure of U.S. Patent No. 5,225,212 to Martin *et al.* [hereinafter "Martin"].

Claims 1-3 and 5-24 were rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure of Paul in view of the disclosure of Martin, in further view of the disclosures of U.S. Patent No. 5,374,548 to Caras [hereinafter "Caras"], Noda *et al., Biochim. Biophys. Acta 1191*:324-330 (1994) [hereinafter "Noda"], and Keder *et al., J. Immunother. 16:*47-59 (1994) [hereinafter "Keder"], individually or on combination.

Claim 4 was rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure of Paul in view of the disclosure of Martin in further view of the disclosures of Caras, Noda, and Keder, and further in view of the disclosure of Kirby *et al., Bio/Technology*, November 1984, pp. 979-984 [hereinafter "Kirby"].

Claims 26-30 were rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure of Paul in view of the disclosure of Martin in further view of the disclosures of Caras, Noda, and Keder, and further in view of the disclosure of U.S. Patent No. 5,612,057 to Lanza *et al.* [hereinafter Lanza"].

Claims 15-24 were rejected under the judicially-created doctrine of obviousness type double patenting in view of claims 1-2 and 4-6 in U.S. Patent No. 6,197,333. Likewise, claims 15-24 were rejected under the judicially-created doctrine of obviousness type double patenting in view of claims 1-14 in U.S. Patent No. 6,348,214.

III. Patentability Arguments

A. The Rejection of Claims 1 -24 and 26-30 under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1-24 and 26-30 under 35 U.S.C. §112, second paragraph, for assertedly failing to particularly point out and distinctly claims the subject matter. The Examiner asserted that it was unclear in claim 1 as to whether the VIP/GRF or IL-2 family of peptides are the active agents which are effective in treating numerous disease

states recited in claim 1, and it was unclear as to what was intended by the term 'feeding disorder.' The Examiner also asserted that claim 3 was unclear as to how one can form multivesicular liposomes by mixing the lipid components as recited in claim 3. The Examiner also asserted that claim 15 should have the word 'products' removed, because it would appear that the liposomes have the recited sizes and not the final products. The Applicants respectfully disagree.

First, the Applicants submit that claim 1 as originally filed was clear; however, in order to expedite prosecutions, claim 1 has been amended to point out that the VIP/GRF or IL-2 family of peptides (including fragments and analogs thereof) are the active agents used in the treatment of the recited disease state. Thus, this rejection as it pertains to this aspect of claim 1 is rendered moot in view of the amendment.

Second, the Applicants submit that the term 'feeding disorder' in claim 1 is a term that is known to one of skill in the art. A feeding disorder is characterized by the failure to eat enough, as reflected by weight loss or a failure to gain weight. A feeding disorder is not caused by a medical condition such as cleft palate, congenital heart disease, chronic lung disease, or a mental condition such as any disorder that causes mental retardation. As described above, a feeding disorder is defined in MEDLINE plus® Health Information's on-line medical encyclopedia (http://www.nlm.nih.gov/medlineplus/) (*see* Exhibit A).

As stated in the specification (*see* page 4, lines 4 through 8), "Some human diseases today are known to be associated with the deficiency in the release of VIP. The deficiency of VIP has been linked to the pathogenesis of several diseases, such as cystic fibrosis, diabetic impotence, congenital mengacolon in Hirschsprung's disease, and achalasia of the esophagus." Achalasia is the constriction of the lower portion of the esophagus due to inability of the sphincter muscles to relax, as defined in CancerWEB's On-line Medical Dictionary (http://cancerweb.ncl.ac.uk/omd/) (*see* Exhibit B). This relaxation is needed to allow food to enter the stomach. As such, this condition is one of the 'feeding disorders' taught in the specification.

Third, the Applicants submit that claim 3 is not unclear. Claim 3 simply claims that a method of treating a disease wherein the liposome composition in the method of claim 1 comprises multivesicular liposomes. The Applicants note that step (b) in claim 1 requires only formation of liposomes. Claims 2 and 3 indicate that these liposomes may be

either unilamellar or multivesicular, respectively, and it is well-known in the art how to carry out steps required to produce either.

Last, the Applicants submit that claim 15 is not unclear as written. However, in order to expedite prosecution of the application, claim 15 and its dependent claims, 16, 19, 20, and 26 have been amended to remove the word 'products' from the term 'liposome products'.

As a result of the amendment and the remarks provided herein, the rejection of claims 1-24 and 26-30 under 35 U.S.C. §112, second paragraph, should be withdrawn.

B. The Rejection of Claims 1-3 and 5-24 under 35 U.S.C. §103(a)

Claims 1-3 and 5-24 were rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure Paul in view of the disclosure of Martin. Claims 1-3 and 5-24 were further rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure Paul in view of the disclosure of Martin, and further in view of the disclosures of Caras, Noda, and Keder, individually or taken together.

The Examiner asserted that the disclosure of Paul describes liposomal compositions containing VIP to be used for the treatment of diseases such as ischemia and mental conditions. However, as noted by the Examiner, these liposomes are not sterically stabilized; the phospholipid is not bound to PEG. The Examiner also asserted that the disclosure of Martin describes preparation of liposomes wherein a lipid component is bound to a water soluble polymer, but, acknowledges that the reference does not teach that drugs can be loaded following liposome formation. The Examiner further asserted that the inclusion of PEG taught by Martin in the liposomes taught by Paul for the preparation of liposomes containing VIP and the use of these liposomes for the treatment of disease states such as ischemia would have been obvious to one of ordinary skill in the art. The disclosure of Caras is asserted to demonstrate that drugs can be loaded on a preformed liposome, and, similarly, the disclosure of Noda is asserted to disclose that VIP can be loaded on preformed liposomes. The disclosure of Keder was cited for disclosing a process of preparation of liposomes and incubating the liposomes (i.e., loading) with IL-2. The Examiner asserted that it would have been obvious to one of ordinary skill in the art to add a drug to the preformed

liposomes of Martin with the expectation of obtaining similar results since Martin teaches that liposomes can be made by any art known method, and the references of Caras, Noda, and Keder show that the liposome formulations and technique of such loading are art known. The Applicants respectfully disagree.

When obviousness is based on a particular prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference. *B.F. Goodrich Co. v. Aircraft Braking Systems Corp.*, 72 F.3d 1577, 1582 (Fed. Cir. 1996). The critical inquiry is whether 'there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.' *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1566 (Fed. Cir. 1983). The Applicants submit that nothing in the cited references suggests the combination comprising the present invention, much less its desirability.

The disclosure of Paul describes liposomal compositions containing VIP to be used in the treatment of diseases, but is silent with respect to VIP with a sterically stabilized liposome. Thus, there would be no expectation of success that a sterically stabilized liposome composition with VIP would be biologically active, because PEG may interfere with VIP/receptor binding due to the size of PEG in relation to the size of VIP. It would be simply impossible to predict if VIP would be able to bind to its receptor in this environment.

Paul also incorporates VIP into the liposome during the process of making the liposome, but, as noted by the Examiner, Paul does not disclose the addition of VIP after the formation of the liposomes. The disclosure of Martin describes preparation of liposomes wherein a lipid component is bound to a water-soluble polymer, but is silent with respect to any method of loading vesicles with drugs after liposome formation. There is no teaching that a biologically active compound can be loaded after the liposome is formed. Likewise, it would be impossible to predict whether the addition of an amphipathic compound to a preformed sterically stabilized liposome would even permit loading of the amphipathic compound in a useful form. Neither reference, therefore, teaches that loading a compound to a preformed sterically stabilized liposome is desirable or even attainable.

As set out above, neither Paul nor Martin disclose or suggest that loading a compound to a preformed sterically stabilized liposome is desirable or even attainable. The disclosure of Caras describes covalently attaching to a preformed liposome a compound with

a glycophosatidylinositol (GPI) signal, but the disclosure is silent with respect to use of sterically stabilized liposomes in this process. The disclosure of Noda describes loading of VIP to a preformed liposome, but the disclosure does not suggest the use of sterically stabilized liposomes. Moreover, the reference is silent as to whether the resulting VIP/liposome compositions are biologically active (with respect to the ability of VIP to bind to its receptor). As discussed above, the disclosure of Keder provides encapsulation of compounds within liposomes, but there is no discussion of a liposome prepared by the steps of (i) preparing liposomes and (ii) loading compounds to the already formed liposome. None of the cited references, alone or in combination, however, teaches or suggests that loading a compound to a preformed sterically stabilized liposome would result in a biologically active product.

One of the essential features of the present invention is that the liposomes must be sterically stabilized (wherein at least one lipid component of the bilayer is attached to a water soluble polymer). Moreover, the resulting liposome must be *biologically active* with respect to the compound that is subsequently loaded. Regardless of the disclosures of Noda and Caras, there is no indication that these same compounds would be active if one or more of the lipids of the bilayer is bound to a polymer. Polymer attachment to a liposome necessarily gives rise to steric hindrance, as well as physical changes in the localized environment at the immediate exterior of the liposome. Whether or not a compound residing in this polymer-rich environment would maintain a proper biological conformation, or be able to interact with a biological ligand, is not predictable, and neither Noda nor Caras suggests that such a liposome composition would be biologically active. As a result, the worker of ordinary skill would not be motivated to make the present claimed invention based on a reading of the cited references, nor would the result be predictable, thereby precluding any expectation of success.

The combination of the references cited by the Examiner may individually include one or more of the elements of the presently claims invention, but none of the references suggests implicitly or expressly that the various teachings should be selected and combined to produce the presently claimed methods of using liposomes, much less that such liposomes would be biologically active. As a result, the rejections of claims 1-3 and 5-24 under §103(a) must be withdrawn.

C. The Rejection of Claim 4 under 35 U.S.C. §103(a)

Claim 4 was rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure of Paul in view of the disclosure of Martin, and further in view of the disclosures of Caras, Noda, and Keder, further in view of the disclosure of Kirby.

The disclosures of Paul, Martin, Caras, Noda, and Keder were cited for reasons described above. The Examiner asserted that the method in the disclosure of Martin does not involve dehydration and rehydration of the liposomes; however, the Examiner asserted that Kirby teaches a method of preparation of liposomes by dehydrating the lipid vesicles and then rehydrating them, resulting in uniform-sized liposomes and that the method is simple and can be used on an industrial scale. Therefore, the Examiner asserted that the introduction of the dehydration-rehydration procedure in the method of preparation of liposomes of Martin would have been obvious to one of ordinary skill in the art because of the advantages of such a step taught by Kirby. The Applicants respectfully disagree.

The standard for a rejection under 103 is set forth in Section B. above; the cited references must suggest or imply the desirability of combining the teachings of the references to produce the claimed invention. As discussed above, none of the disclosures of Paul, Martin, Noda, Caras, or Keder suggests the liposome composition as recited in claim 4 and the disclosure of Kirby does not correct this defect. Kirby fails to disclose use of a liposome that is sterically stabilized, much less loaded with a targeting component. There is also no teaching that a targeting component can be attached after the liposome is formed. As discussed above, the addition of polymers to the exterior of a liposome alters the localized environment, and as a result, it would be impossible to predict whether a targeting agent in the polymer environment would be able to identify and/or interact with its natural target ligand and therefore be biologically active.

The combination of the references, therefore, fails to suggest the method of claim 4. Because of the unpredictable utility of these compounds, the worker of ordinary skill would not be motivated to produce these compounds and the cited references fail to overcome this unpredictability. Likewise, there would be no expectation of success. The Applicants therefore submit that the rejection of claim 4 under §103(a) is improper and must be withdrawn.

D. The Rejection of Claims 26-30 under 35 U.S.C. §103(a)

Claims 26-30 were rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure of Paul in view of the disclosure of Martin, and further in view of the disclosures of Caras, Noda, and Keder, further in view of the disclosure of Lanza.

The Examiner asserted that the disclosures of Paul, Martin, Caras, Noda, and Keder do not teach a diagnostic method using liposomes; however, the Examiner asserted that the use of liposomes in the diagnostic methods of claims 26-30 would have been obvious to one of ordinary skill in the art, with the expectation of obtaining similar results, since the disclosure of Lanza shows the routine use of liposomes for diagnostic purposes. The Applicants respectfully disagree.

As discussed above, none of the disclosures of Paul, Martin, Noda, Caras, or Keder suggests the liposome composition as recited in claims 26-30 and the disclosure of Lanza does not correct this defect. Lanza fails to disclose use of a liposome that is sterically stabilized, much less loaded with a targeting component. There is also no teaching that a targeting component can be loaded after the liposome is formed. As discussed above, the addition of polymers to the exterior of a liposome alters the localized environment, and as a result, it would be impossible to predict whether a targeting agent in the polymer environment would be able to identify and/or interact with its natural target ligand.

None of the references suggests or implies any diagnostic purposes for the liposome compositions described therein, and as a result, the cited references are wholly unrelated to the subject matter of claims 26-30. The combination of the references, therefore, fails to suggest the diagnostic liposomes of claims 26-30. Because of the unpredictable utility of these compounds, the worker of ordinary skill would not be motivated to produce these compounds and the cited references fail to overcome this unpredictability. The Applicants therefore submit that the rejection of claims 26-30 under §103(a) is improper and must be withdrawn.

E. The Rejection for Obviousness-Type Double Patenting

Claims 15-24 were rejected under the judicially-created doctrine of obviousness type double patenting in view of claims 1-2 and 4-6 in U.S. Patent No. 6,197,333. Likewise, claims 15-24 were rejected under the judicially-created doctrine of obviousness type double patenting in view of claims 1-14 in U.S. Patent No. 6,348,214.

In response, the Applicants submit that a rejection under the judicially-created doctrine of obviousness type double patenting may only be made with a comparison of the claims in this application and the cited patents, not the specifications (*see* MPEP § 804). The claims in the cited patents, parent applications to the instant application, do not suggest the presently claimed invention, specifically because all the elements of the presently claimed invention are not found in the cited claims from U.S. Patent Nos. 6,197,333 and 6,348,214.

Therefore, the rejection under the judicially-created doctrine of obviousness type double patenting is improper and should be withdrawn.

SUMMARY

In view of the amendments and remarks made herein, the Applicants believe that claims 1-31 are in condition for allowance and request expedited notification of the same.

Respectfully submitted,
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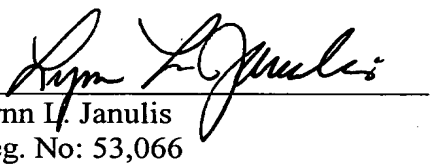
By: 
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Feeding disorder of infancy and early childhood

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Contents of this page:

Definition

A feeding disorder of infancy or early childhood is the failure of a young child to obtain adequate nutrition, which is reflected by weight loss or a failure to gain weight appropriately for development.

Causes, incidence, and risk factors

Feeding disorders are diagnosed when the infant or young child appears malnourished and the problem is not caused by a medical condition (such as cleft palate, congenital heart disease, or chronic lung disease), or a mental condition (such as any disorder that causes mental retardation).

The cause of these disorders is often unknown, but they often result from a variety of factors such as poverty, dysfunctional child-caregiver interactions, or parental misinformation about appropriate diet to meet the child's needs.

Symptoms

- Poor weight gain
- Weight loss
- Constipation
- Excessive crying
- Irritability
- Apathy

Signs and tests

Physical examination is performed to evaluate for any medical illness that could cause or contribute to the problem. Evaluation of the growth curves for height, weight, and head circumference are important in any evaluation of feeding or weight problems.

Laboratory and imaging studies may be used to complete the medical workup but often are normal in children with growth problems.

Treatment

Depending on the severity of the condition, the following measures may be taken:

- Increase the number of calories and amount of fluid the infant takes in
- Correct any vitamin or mineral deficiencies
- Identify and correct any underlying physical illnesses or psychosocial problems

A short period of hospitalization may be required to accomplish these goals.

Expectations (prognosis)

There is no quick cure for the majority of infants and children with feeding disorders. Instead, a multidisciplinary approach is required with pediatricians, outreach nurses, dietitians, social workers, behavior specialists, and parents working together to improve the child's well-being and nutritional status.

Complications

Childhood malnutrition can permanently stunt mental and physical development if it is severe and long-lasting. Early treatment can prevent such complications.

Calling your health care provider

Call for an appointment with your pediatrician if you have concerns about your child's appetite, behavior, development, or growth.

Prevention

Following recommended guidelines for nutrition can help ensure adequate caloric and fluid intake for an infant. Regular well-child visits to your pediatrician can help identify any feeding and growth problems early and can prevent permanent damage related to malnutrition.

Update Date: 12/22/2002

Updated by: Philip L. Graham III, M.D., F.A.A.P., Department of Pediatrics, Children's Hospital of New York, Columbia University, New York, NY. Review provided by VeriMed Healthcare Network.

achalasia

<gastroenterology> Constriction of the lower portion of the food pipe (oesophagus) due to inability of the sphincter muscles to relax.

Symptoms include difficulty swallowing, chest pain, vomiting and heartburn.

Treatment includes oesophageal dilation using special instruments or medications (for example nitroglycerin, calcium channel blockers).

(27 Sep 1997)

Previous: acetyl transacylase, acetyltransferase, acetyltransferases, acetyl value, A chain
Next: Achard, E. Charles, Achard syndrome, Achard-Thiers syndrome, achate